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A Comprehensive analysis of the impact of *Pseudomonas aeruginosa* colonisation on prognosis in adult bronchiectasis

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Rationale:

Eradication and suppression of *Pseudomonas aeruginosa* is a key priority in national guidelines for bronchiectasis, and is a major focus of drug development and clinical trials. An accurate estimation of the clinical impact of *P. aeruginosa* in bronchiectasis is, therefore, essential.

Methods

Data from 21 observational cohort studies comparing patients with *P. aeruginosa* colonisation to those without were pooled by random effects meta-analysis with data collected for key longitudinal clinical outcomes of mortality, hospital admissions, exacerbations and lung function decline along with cross sectional outcomes such as quality of life.

Measurements and main results:

Studies included 3683 patients. *P. aeruginosa* was associated with a highly significant and consistent increase in all markers of disease severity including mortality (odds ratio (OR) 2.95, 95% CI 1.98-4.40; p<0.0001), hospital admissions (OR 6.57, 95% CI 3.19-13.51; p<0.0001) and exacerbations (mean difference 0.97 per year, 95% CI 0.64-1.30; p<0.0001). Patients with *P. aeruginosa* also had worse quality of life using the St Georges Respiratory Questionnaire (mean difference 18.2 points, 95% CI 14.7-21.8; p<0.0001). There were also large differences in lung function and radiological severity.

Definitions of colonisation were inconsistent but findings were robust irrespective of the definition used.

Conclusion: *P. aeruginosa* is associated with an approximate 3-fold increased risk of death and an increase in hospital admissions and exacerbations in adult bronchiectasis.

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Introduction

Bronchiectasis is a chronic inflammatory lung disease characterised by recurrent cough, sputum production and recurrent respiratory tract infections.(1) Failure of the mucociliary escalator and innate antimicrobial defences leads to chronic bacterial colonisation of the airways.(2) Bacteria provoke an inflammatory response that can further drive airways inflammation and airway structural damage leading to the well described "vicious cycle" of bronchiectasis.(2,3)

While the majority of patients with bronchiectasis may be colonised with organisms that are upper airway commensals such as *Haemophilus influenzae* and *Streptococcus pneumoniae,* a proportion of patients become colonised with the opportunistic pathogen *Pseudomonas aeruginosa.*(4-6)

In cystic fibrosis (CF) bronchiectasis, it is well established that *P. aeruginosa* colonisation leads to a more rapid deterioration in lung function and earlier mortality.(7) Consequently, *P. aeruginosa* eradication is standard care in European CF centres.(8,9) The capability of *P. aeruginosa* to form biofilms provide it with physical and chemical protection from the immune system and reduces its exposure to systemically delivered antibiotics.(10,11) *P. aeruginosa* has the ability to rapidly adapt to chronic infection in the lung and readily develops antimicrobial resistance. Management of *P. aeruginosa* therefore represents a significant clinical challenge.

In bronchiectasis, conflicting data have been published on the independent contribution of *P. aeruginosa* to long term prognosis and there remains a question of whether *P. aeruginosa* drives disease progression or is simply a marker of existing severe disease.(12,13) Determining the importance of *P. aeruginosa* to bronchiectasis morbidity and mortality is important, as there are few evidence based treatments for bronchiectasis.(14) Current therapeutic development is heavily influenced by CF and is therefore largely targeted towards treatment of *P. aeruginosa* infection.(15,16) Therefore from clinical, drug development and regulatory perspectives it is important to have a comprehensive understanding of the impact of *P. aeruginosa* on outcomes in bronchiectasis.

We therefore undertook a systematic review to determine whether colonisation with *P. aeruginosa* influences future prognosis and/or is associated with cross-sectional features of severity.

METHODS

The present study was a systematic review and meta-analysis conducted and reported according to MOOSE (meta-analysis of observational studies in epidemiology) guidelines.(17)

Search Criteria

The study was based on a search of the PUBMED database for articles evaluating the prognostic impact of colonisation with *P. aeruginosa*. The following search strategy was used: ("Pseudomonas" OR "aeruginosa") AND ("bronchiectasis") followed by (“prognosis” or “mortality”) and (“bronchiectasis”). The search included articles published between January 1980 and January 2015. No language criteria were applied. Full articles of potentially appropriate abstracts were reviewed. Only peer reviewed data were included. Conference abstracts were excluded. The search was repeated in EMBASE and Web of Science to obtain any articles missed by the initial search. The search strategy was supplemented by reviewing of the reference lists, bibliographies including the British Thoracic Society guidelines and investigator files.

Data extraction

Non relevant studies were excluded based on review of the title and abstract. Article reviewing was performed independently by two investigators ((two out of SF, ,MM, AHL, SA and JC) who conducted data extraction and quality assessment from studies meeting the inclusion criteria. All investigators have experienced of meta-analysis and training in literature review. Any disagreement between investigators was resolved independently by a third investigator. Additional unpublished data were obtained from study authors where possible. Where data were presented only as medians, means with standard deviation were estimated according to the formula of Hozo et al.(18)

Study inclusion and exclusion criteria

All studies were considered eligible if they fulfilled the following criteria: original publications; inclusion of a cohort of patients with computed tomography diagnosed bronchiectasis not due to cystic fibrosis; inclusion of patients with *P. aeruginosa* colonisation and a comparator population without *P. aeruginosa* colonisation; reporting of one of the study outcomes which were determined *a priori* (described below).

Definitions of *P. aeruginosa* colonisation were obtained from the source studies and were not pre-specified.

As the aim of this study was to compare *P. aeruginosa* colonised patients compared to non-colonised patients, we excluded any studies which provided data only for a single population. We also excluded case reports; review articles, editorials and letters without original data.

Study outcomes

Primary analysis

Our hypothesis was that *P. aeruginosa* colonisation would be associated with globally worse clinical outcome when compared to patients without *P. aeruginosa* colonisation. Outcomes were split into longitudinal clinical outcomes determined during follow-up, and cross-sectional outcomes. The primary longitudinal outcome was all-cause mortality. Secondary outcomes were: hospital admissions, exacerbation frequency, decline in forced expiratory volume in 1 second (FEV_1) and the prognostic impact of *P. aeruginosa* eradication therapy.

Cross sectional outcomes were: FEV_1 % predicted, forced vital capacity (FVC), radiological involvement and quality of life (QoL). A descriptive analysis of the methods of defining *P. aeruginosa* colonisation in the literature was also considered a pre-specified secondary end-point.

Anticipating that studies would have different lengths of follow-up to determine survival, we pre-specified that data could be pooled where equal follow-up was demonstrated between P. aeruginosa colonised and non-colonised patients.

Quality assessments

The quality of each study was independently assessed according to the criteria described by Hayden et al, which are widely used for assessing the quality of observational studies in meta-analysis.(19,20) The agreement between the two reviewers (two of SF, AHL and JC) was measured using the kappa statistic. Publication bias was determined by visual inspection of funnel plots and Eggers test.

Sensitivity analysis

A priori we identified possible factors that may be major sources of bias and planned subanalyses for the follow; 1) Analysis according to different definitions of *P. aeruginosa* colonisation e.g single isolate versus multiple isolatins; 2) Comparison of *P. aeruginosa* vs *H. influenzae* colonised patients compared to comparisons of *P. aeruginosa* colonised vs non-colonised patients; 3) Data derived from high quality and prospective studies.

Statistical analysis

The primary outcome of the relationship between *P. aeruginosa* colonisation and mortality was displayed as odds ratios (OR) with 95% confidence intervals (95% CI). ORs were pooled using a Mantel-Haenszel random effects model. The same analysis was used for hospital admissions.

Continuous variables such as quality of life, lobar involvement, pulmonary function tests and exacerbations were compared by pooling mean differences by the inverse of their variance. As above, random effects meta-analysis was used due to expected heterogeneity between studies. To analyse for possible effect modifiers, such as study quality or definitions of colonisation, we compared OR's using interaction testing as described.

Statistical heterogeneity was assessed using the Cochran Q (χ^2) test and the Higgins I^2 tests. For the Cochran Q test, $p<0.1$ was considered to represent significant heterogeneity. For the Higgins test, I^2 <25% indicated low heterogeneity, 25–50% moderate and >50% severe heterogeneity. Analyses were conducted using Review Manager 5 (Cochrane Collaboration) and SPSS version 21 for windows (Chicago, IL, USA).

RESULTS

The results of the literature review are shown in figure 1. The majority of studies were rejected because they did not deal specifically with patients with bronchiectasis not due to CF or did not evaluate severity or outcomes. Of 55 articles selected as relevant, 21 studies had valid data for inclusion and were pooled in the meta-analysis.(6,12,13,21-36) One study contained data for 5 cohorts and each cohort was considered separately for the purposes of this analysis on the basis that they were independent cohorts (total 25 cohorts).(24)

Characteristics of the 21 included studies are shown in table 1. 10 studies were from the UK (12,21,23,24,26,28,31,32) and overall 16 cohorts were from Europe. There were no cohorts from North America.

Definitions of chronic *P. aeruginosa* colonisation were highly heterogeneous. The most frequent definition used was 2 positive cultures at least 3 months apart over 12 months. 5 studies reported patients with a single positive culture as “colonised”. In all, 8 different methods of defining *P. aeruginosa* colonisation were identified in addition to 3 studies where the definition was not stated. According to the quality assessment, 6 studies were rated as high quality, 8 as intermediate, and 7 as low quality (Kappa 0.73). None of the analyses showed evidence of publication bias.

The total number of patients studied was 3683 with a rate of *P. aeruginosa* colonisation (according to study definitions) of 21.4%. Comparator populations were almost universally mixed populations of bronchiectasis not colonised with *P. aeruginosa*.

Impact of *P. aeruginosa* on longitudinal outcomes

Primary outcome: All-cause Mortality

Mortality was available as an outcome in 8 cohorts (24-27) of which 5 cohorts were derived from a single study (24). Follow-up duration ranged from 1 year to 14 years. Mortality for patients with *P. aeruginosa* ranged from 7.7% at 1 year, 13.6% at 2 years to 30-50% at 5 years. Corresponding mortality rates for patients without *P. aeruginosa* were 0% at 1 year, 7% at 2 years and 9-15% at 5 years. All studies showed a higher risk of mortality associated with *P. aeruginosa* colonisation. The pooled OR for mortality was 2.95 (95% CI 1.98-4.40; p<0.0001). Heterogeneity tests were not statistically significant. This is shown in figure 2.

Sub-analyses confirmed this association in high quality studies (OR 3.64, 95% CI 1.75-7.55; p=0.0005, n=1433), prospective studies and excluding studies with <3 (OR 2.82, 95% CI 1.94-4.11; p<0.0001, n=1994) and >6 years follow-up (OR 3.14, 95% CI 1.83-5.33; p<0.0001, n=1894).

Hospital admissions

This analysis included 7 cohorts with 1628 participants (23,24,29). Hospital admission rates for patients with *P. aeruginosa* varied from 41% at 1 year to 75% at 4 years. Corresponding hospital admission rates in patients without *P.* aeruginosa were 15% at 1 year and 28.5% at 4 years. P. *aeruginosa* was associated with a marked increase in the risk of hospital admissions – pooled OR 6.57 (95% CI 3.19-13.51; p<0.0001). There was significant heterogeneity which was not resolved on limiting studies by quality, prospective design or length of follow-up. Insufficient data was available to evaluate additional impacts such as length of hospital stay or economic impacts of hospitalisation. Data are shown in figure 3.

Exacerbations per year

All available data were presented as mean exacerbations per patient per year. The 9 cohorts which recorded this information gave a pooled increased frequency of just under 1 exacerbation per patient per year – mean difference 0.97 (95%CI 0.64-1.30; p<0.0001) with no significant heterogeneity.(6,23,24,29,30) This is shown in figure 4. No significant differences in effect were observed in high quality studies, prospective studies or in sub-analyses based on the definition of *P. aeruginosa*.

Lung function decline

There were limited data available on lung function decline. One study reported lower lung function in PA colonised patients but no differences in long term lung function decline.(13) Another study reported a mean decline of 52ml per year in *P. aeruginosa* patients(12) with a further study reporting a mean decline of 123ml per year.(38) The available data included only 41 patients with *P. aeruginosa* colonisation. Consequently no attempt was made to pool the data.

Pseudomonas eradication treatment

No randomised studies of *P. aeruginosa* eradication treatment were identified. A non-randomised observational study (n=30) reported an initial eradication success rate of 80%, and 43% after a median of 6 months.(39) This was associated with a reduction in exacerbations from 3.93 per year to 2.03 per year. No control population was available for comparison with no data on the spontaneous clearance rate that would have occurred without treatment.

Cross sectional association between P. aeruginosa and markers of severe disease

Patient characteristics

In cross-sectional studies we observed that patients with *P. aeruginosa* infection were on average 3 years older than non-colonised patients (mean difference 3.1 years, 95% CI 0.9-5.4,p=0.007, I^2=48%). Interestingly there was a statistically significant association between male gender and *P. aeruginosa* colonisation, OR 1.39 95% CI 1.09- 1.75, p=0.009, I^2=0%.

Quality of life

The only data that were available for QoL used the St.Georges Respiratory Questionnaire (SGRQ). The SGRQ is a validated questionnaire in patients with bronchiectasis that has been widely used with an accepted increment of 4 points demonstrating clinical significance.(37) 4 studies reported data for SGRQ, with a mean difference of 18.2 points (95% CI 14.7-21.8; p<0.0001, n=1041).(22,24,28) There was no heterogeneity between studies (I^2=0%). No data were available for other questionnaires, including the QoL-Bronchiectasis questionnaire.

Lung Function- FEV_1 and FVC

As expected, patients with *P. aeruginosa* colonisation had worse cross-sectional lung function compared to patients without *P. aeruginosa*. 17 studies reported valid data for FEV_1 with all showing worse lung function in the *P. aeruginosa* group ranging from -1.4% to -29%. (6,12,13,21,22,24,28,29,30,31,33,34,36) The pooled mean difference was 15.0% (95% CI -18.7 to -11.3; p<0.0001). There was significant heterogeneity but this was no longer statistically significant after excluding 1 study that defined *P. aeruginosa* presence by PCR.(6) 9 cohorts presented data for FVC with a pooled mean difference of -9.4% (95% CI -14.3 to -4.5%;p=0.005, n=1453). (12,24,28,29,33,34)

Radiological severity

Although multiple severity scoring systems have been utilised in bronchiectasis, the only variable which was studied in more than one study was the number of lobes involved on CT. This data were available in 9 cohorts.(24,29,30,32,34,35) The mean difference between *P. aeruginosa* colonised and non-colonised was 1.4 lobes (95% CI 0.93-1.86; p<0.0001). Nevertheless all studies reported worse radiological severity in *P. aeruginosa* colonised patients.

Sensitivity analyses

Limiting the analysis to only those studies that used the most robust definition of *P. aeruginosa* colonisation, requiring at least 2 positive sputum samples over a 12 month period, showed very similar results to the primary analysis with ORs for mortality of 3.46, 95% CI 1.96-.6.08; p<0.0001; hospital admissions 7.22, 95% CI 2.88-18.09; p<0.0001 and exacerbations mean difference 0.87, 95% CI 0.59-1.15; p<0.0001 (p>0.5 when comparing odds ratios using interaction testing compared to the overall cohort).

8 cohorts provided data that could be used to directly compare the outcomes of patients colonised with *P. aeruginosa* versus *Haemophilus influenza*e. The findings were highly consistent with the main analysis, with an increase in mortality associated with *P. aeruginosa* (OR 4.00, 95% CI 2.28-7.02; p<0.001), increased rate of hospital admissions (OR 6.75, 95% CI 3.98-11.45; p<0.001), increased exacerbations (mean difference 0.99 (95% CI 0.54-1.43; p<0.0001) and low FEV_1 (mean difference -11.4, 95% CI -14.8 to -7.9; p<0.0001).

DISCUSSION

The management of bronchiectasis patients with *P. aeruginosa* colonisation is challenging and a large proportion of the current therapeutic development in bronchiectasis is focussed towards management of *P. aeruginosa* infection.(14-16) In particularly there are intensive efforts in the field of inhaled antibiotics to develop a licensed therapy for *P. aeruginosa* infection in bronchiectasis.(15,16) Therefore an accurate assessment of the prognostic impact of *P. aeruginosa* in bronchiectasis is important for clinicians, for drug developers and for regulators. This analysis provides a detailed insight into the impact that *P. aeruginosa* colonisation has on key clinical outcomes in bronchiectasis. In addition, *P. aeruginosa* colonisation was associated with multiple cross-sectional markers of disease severity. It can therefore be said that *P. aeruginosa* is both a marker of severe disease, and is associated with a worse long term prognosis. Bronchiectasis has historically been a neglected condition, described in the ERS white book as one of the most neglected diseases in respiratory medicine.(40) As a result, there have been few large cohort studies. The value of meta-analysis therefore is to combine the available data from existing small studies to give a more accurate estimate of the disease impact.

The most striking finding within this analysis is the impact of *P. aeruginosa* on all-cause mortality. Our analysis identifies a 3-fold increase in the risk of death with *P. aeruginosa* colonisation. *P. aeruginosa* was also associated with a greatly increased the risk of hospital admissions and exacerbation frequency by a rate of 1 exacerbation per patient per year. This finding was robust regardless of the definition used and was consistent across all cohorts. These results strengthen the view that patients with P. aeruginosa require specific treatment to reduce the risk of long term morbidity and mortality and that *P. aeruginosa* colonisation status should play a key role in the assessment of disease severity.(14)

The increased exacerbation frequency and hospital admissions demonstrates a measurable healthcare cost associated with *P. aeruginosa* colonisation. Each additional exacerbation results in further antibiotic use with associated risks and side-effects as well as increased potential for the development of antimicrobial resistance. Exacerbations are associated with reduced productivity through absence from work and are associated with poorer QoL and potential lung function decline.(24,38,41) Hospital admissions may reflect more severe exacerbations or the development of resistance to oral antibiotic agents necessitating intravenous antibiotic therapy.(24) The ability of *P. aeruginosa* to develop antibiotic resistance is inevitably enhanced by repeated antibiotic exposure.(29)

Our analyses of quality of life, lung function and radiological severity were cross-sectional and can therefore only be considered hypothesis generating in terms of the impact of *P. aeruginosa* on these outcomes over the long term. Nevertheless the impact on QoL demonstrated in this analysis is striking. The 18 point decrement in the SGRQ demonstrated in patients with *P. aeruginosa* colonisation reflects a dramatic worsening of QoL. Given our observation that patients with *P. aeruginosa* had reduced lung function and more widespread radiological disease on imaging it is difficult to determine what proportion of this difference in QoL is directly attributable to *P. aeruginosa*. All of the analyses described herein are subjective to the same limitation, that *P. aeruginosa* may be to some extent a reflection of the severity of underlying disease rather than a directly cause of disease progression. The only way to conclusively prove or quantify the independent effects of *P. aeruginosa* on outcome is likely to be through a large randomised controlled trial of *P. aeruginosa* eradication treatment which has been highlighted as a clear priority for the bronchiectasis research community.(42) Demonstrating that mortality, hospital admissions, exacerbations, QoL and lung function are improved or cease to decline after successful eradication would clearly demonstrate the independent impact of *P. aeruginosa*. A strength of our analysis is that it provides the most precise estimates to date of *P. aeruginosa* prevalence and impact in order to power future trials.

Current national guidelines for bronchiectasis recommend eradication treatment for new isolation of *P. aeruginosa*, largely based on recommendations for CF.(8,14,43) Data in bronchiectasis is limited to date and further research is greatly needed.

Important gaps in the literature identified through this analysis include an absence of data available outside Europe and Australasia with a large proportion of included data from the UK; broad, representative registries for patients with bronchiectasis are needed internationally. Few studies examining lung function decline were identified, and those that were found were small with inconsistent results. We would recommend further large studies of lung function decline in bronchiectasis. There is a lack of data describing the impact of organisms other than *P. aeruginosa* in bronchiectasis and in particular comparing the outcomes of *P. aeruginosa* colonised patients with those colonised with the most common bronchiectasis pathogens such as *H. influenzae or Moraxella catarrhalis*. Such data would be valuable as recent reports suggest that these patients do have a worse outcome compared to non-colonised patients, but to a lesser extent than *P. aeruginosa*.(24) For example in the Bronchiectasis Severity Index, 3 points are awarded to patients with *P. aeruginosa* colonisation and 1 point to patients colonised with other pathogens.(24) For this meta-analysis, we were able to identify 8 cohorts with data to compare outcomes between *P. aeruginosa* and *H. Influenzae* colonised patients and these confirmed the significantly worse clinical outcomes associated with *P. aeruginosa.*

There is a need from both a clinical and research perspective to define chronic bacterial colonisation in bronchiectasis as this analysis identified 8 different methods of defining *P. aeruginosa* colonisation in bronchiectasis studies. The most frequently used definition was 2 or more positive cultures at least 3 months apart in 12 months. This should be standardised across studies to increase our ability to generalise results between studies and healthcare systems. Our data were almost entirely based on traditional bacterial culture and recent studies have increasingly used quantitative PCR or characterisation of the microbiome through sequencing of the 16s ribosomal RNA subunit to determine bacterial colonisation status.(6,36,44) This method is significantly more sensitive for the detection of *P. aeruginosa* with Rogers et al. demonstrating very poor correlation between culture and PCR for *P. aeruginosa* detection: 91/107 patients in this study were positive for *P. aeruginosa* versus 31/107 by culture.(6) For this reason, further studies of the role of PCR in *P. aeruginosa* detection and to confirm eradication, would be beneficial.

The word colonisation in this context is perhaps misleading. Colonisation implies a benign state defined by absence of tissue invasion or tissue damage. The term 'chronic infection' may be more appropriate given the clearly established association between the presence of bacteria and airway inflammation and the worse clinical outcomes observed in the presence of *P. aeruginosa*.

In summary, *P. aeruginosa* colonisation is associated with increased mortality, hospital admissions and exacerbations, and is associated with worse QoL. As such, new Isolation of *P. aeruginosa* should be considered a highly significant clinical event and followed up with repeated cultures and attempts to eradicate in line with guideline recommendations.

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Figure 1. Flow chart illustrating the process and results of the literature review. Abbreviations: QoL= quality of life; FEV_1= forced expiratory volume in 1 second.

Figure 2. Association between *P. aeruginosa* colonisation and mortality in bronchiectasis. Abbreviations: OR= odds ratio, M-H= Maentel-Haentzel, IV= inverse variance, CI= confidence interval,

Figure 3. Association between *P. aeruginosa* colonisation and hospital admissions in bronchiectasis. Abbreviations: OR= odds ratio, M-H= Maentel-Haentzel, IV= inverse variance, CI= confidence interval

Figure 4. Exacerbation frequency comparing patients with and without *P. aeruginosa* colonisation. Abbreviations: OR= odds ratio, M-H= Maentel-Haentzel, IV= inverse variance, CI= confidence interval

Figure 5. FEV_1 % predicted compared between patients with *P. aeruginosa* colonisation and patients without *P. aeruginosa* colonisation. Abbreviations: OR= odds ratio, M-H= Maentel-Haentzel, IV= inverse variance, CI= confidence interval